anaphylactic reactions, but there is no relationship between these reactions and hypersensitivity to sulfonamides. Patients who have had allergic reactions to sulfonamide drugs do not need to avoid sulfites, sulfates or sulfur.

Conclusion

As a general principle, all allergic adverse reactions to medications should be recorded in the patient's file with the specific name of the drug or drugs to which the patient has reacted and the nature of the reaction. Allergies should not be attributed to classes or groups of drugs unless proven because assumptions about cross-reactivity may later be found to be incorrect. The term 'sulfur (or sulphur, sulpha, sulfa) allergy' should not be used.

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Further reading

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 27)

3. A patient who has an allergic reaction to the combination of trimethoprim and sulfamethoxazole may have a similar reaction to trimethoprim.
4. Patients who are allergic to sulfonamides should avoid food containing sulfites.

Medicinal mishap

Neutropenia with quetiapine

Prepared by Jacqueline Landau, Pharmacy Department, Ken Lu, Department of General Medicine, Cheng Choo, Pharmacy Department, and Peter Greenberg, Department of General Medicine, The Royal Melbourne Hospital

Case

An 85-year-old woman was admitted to hospital with an exacerbation of heart failure secondary to cardiac arrhythmia. Her past history included atrial fibrillation, diastolic heart failure, emphysema, gastritis, Alzheimer's disease and anxiety. She was taking quetiapine, sertraline, donepezil, omeprazole, tiotropium, salbutamol and diltiazem.

Examination revealed rapid atrial fibrillation, with no systemic or focal signs of sepsis, and she was afebrile. Haemoglobin, thyroid function, liver function and serum creatinine were normal. Her chest X-ray showed changes consistent with pulmonary oedema and bilateral pleural effusions. She was treated with frusemide and aspirin.

On the day before admission her white cell count was normal (5.5×10^9/L) with a neutrophil count of 4.1×10^9/L. However, on admission her white cell count was low (2.9×10^9/L with a neutrophil count of 1.9×10^9/L). The day after admission her white cell count fell to 2.7×10^9/L and her neutrophil count to 1.5×10^9/L.

Following a detailed review of all her drugs and in consultation with the psychiatry team, we decided to start risperidone and cease her quetiapine as it could have been the cause of the neutropenia. She had started quetiapine 200 mg twice a day four months earlier for the control of psychotic behaviour related to Alzheimer's disease. Her white cell counts were normal before she started quetiapine.

Five days after admission, the white cell count had increased to 4×10^9/L and the neutrophil count to 2.6×10^9/L (see Table 1). Given her improvement, bone marrow biopsy was not performed. Her psychotic symptoms remained controlled with the switch to risperidone, and she was discharged from hospital.

Comment

Quetiapine is an atypical antipsychotic drug with a similar chemical structure to clozapine and olanzapine. Clozapine was the first atypical antipsychotic drug, but the risk of significant agranulocytosis requires rigorous monitoring.

Table 1

White cell and neutrophil counts

Time of tests	White cell count (x 10^9/L)	Neutrophil count (x 10^9/L)
3 months before admission	4.2	2.6
Day before admission	5.5	4.1
Admission	2.9	1.9
Day 2	2.7	1.5
Day 4	3.9	2.6
Day 6	4.0	2.6
2 months after admission	6.8	4.5

The risk of neutropenia and agranulocytosis associated with antipsychotics such as clozapine is reported to be between 1% and 10%. With quetiapine, premarketing and smaller postmarketing studies suggest the risk of neutropenia is less than 0.01%. By November 2007 the Australian Adverse Drug Reactions Advisory Committee (ADRAC)[1] had received two possible and eight probable case reports of neutropenia associated with quetiapine. Seven of the eight patients were known to have recovered after stopping the drug.

The onset of neutropenia with quetiapine is variable. In the ADRAC series, neutropenia was reported to have occurred from one week to one year after starting therapy. The dose of quetiapine ranged from 50 mg daily to 1000 mg daily. The effect did not appear to be dose dependent. Published case reports include patients who developed neutropenia two days[2] and two months[3] after starting quetiapine. Other reports of quetiapine-associated neutropenia have been confounded by the simultaneous use of clozapine[4] or valproate.[5,6]

The exact mechanism(s) by which quetiapine causes neutropenia is unknown. From the clozapine literature, proposed mechanisms are direct bone marrow suppression or toxicity from the drug or its metabolites.[7] Immmunologically mediated destruction of granulocytes or granulocytic precursors has also been proposed. Given the related chemical structure and pharmacological profile of quetiapine and clozapine, quetiapine-induced neutropenia may have similar mechanisms.[3]

Our patient was taking multiple medications before admission, but sertraline and omeprazole were the only other drugs suspected to cause neutropenia. However, as she had taken sertraline and omeprazole for more than one year, it was thought that quetiapine was the more likely explanation. In addition, after stopping quetiapine, the neutropenia resolved, despite the continuation of both sertraline and omeprazole.

The World Health Organization definition of 'probable/likely' causality assessment of a suspected adverse reaction is:

> a clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition.[8]

Based on these criteria, it appears our patient had a 'probable' response to the development of neutropenia associated with quetiapine, with a rapid recovery after the drug was stopped and replaced by risperidone.

Although the risk of agranulocytosis is low it needs to be balanced against any benefit of treatment. There is currently no strong evidence to support the use of quetiapine for psychological and behavioural problems in patients with dementia.[9]

Conclusion

The risk of agranulocytosis with quetiapine is significantly lower than with clozapine, so regular estimations of white cell and neutrophil concentrations are not indicated. However, vigilance is required, as blood dyscrasias can still occur.

We would like to acknowledge the advice received from Dr Sam Robson, Psychiatric registrar, Royal Melbourne Hospital.

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